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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Application of: HORST PESCHEL			
Conf. No.:	3984	Group Art Unit:	1647
Appln. No.:	09/596,507	Examiner:	Robert Clinton Hayes
Filing Date:	June 16, 2000	Attorney Docket No.:	600574-1 (K400417US)
Title:	Synthetic Neuronal Tissue Derived From Neuronal Progenitor Cells		

DECLARATION OF JOHANNES SCHWARZ

I, Johannes Schwarz, declare and state as follows:

1. I am a founding member of NeuroProgen GmbH Leipzig, the assignee of the above-captioned patent application.

2. I am presently a full professor and vice-chairman of the department of Neurology at the University of Leipzig, Leipzig, Germany. I am also a visiting associate at the California Institute of Technology, Pasadena, California. I hold a degree in medicine from the medical school in Würzburg, and numerous professional certifications in the field of neurology, including Board Certification in Neurology and Neurophysiology, as listed in my *Curriculum vitae*, attached hereto as Exhibit A. I have also published extensively in peer-reviewed publications in the field. Publications representative of my work in the field are provided in Exhibit A.

3. I have reviewed

(i) this patent application,

(ii) the Office Action mailed April 9, 2002 (Paper No. 9),

(iii) the Office Action mailed December 5, 2002 (Paper No. 12),

(iv) the Office Action mailed July 21, 2003 (Paper No. 16),

(v) the Advisory Action mailed November 18, 2003 (Paper No.18).

4. I have reviewed the prior art references United State Patent No. 5,411, 883 of Boss, et al. ("Boss"), and International Patent Application No. WO 97/02049 of Luskin, *et al.* ("Luskin").

5. I am aware that the Examiner has rejected claims 44-49, 51-54, and 58-84 under 35 U.S.C. § 102(b) as being anticipated by Boss and Luskin, each taken individually. Paper No. 12 at 6. I understand that the Examiner contends that Boss teaches human and porcine neuronal progenitor cells, which the Examiner characterizes as "mammalian brain-derived neuronal tissue from the mesencephalon that inherently contain progeny of a single multipotent neuronal stem cell derived from immature stem cells." Paper No. 9 at 6. The Examiner further contends that Boss describes "partial differentiation," "full differentiation," and "select[ion of] individual cells expressing dopaminergic markers," in column 13 and 20. *Id.* The Examiner states that because there is no mention of graft rejection or provocation of an immune response, the cell cultures must not have contained glial cells. *Id.* The Examiner states that the neuronal progenitor cells of Boss are inherently "capable of differentiating." Paper No. 12 at 6. On these bases, the Examiner asserts the claims are anticipated by Boss. *E.g.,* Paper No. 12.

6. I am aware the Examiner has rejected claims 44-49, 51-54, and 58-84 as anticipated by Luskin. Paper No. 12 at 6. The Examiner states that Luskin teaches isolation of human and mammalian brain-derived neuronal progenitor cells that are "capable of differentiating into >90% dopaminergic neurons." He states that "Luskin's progenitor cells [sic] contain less than 2% glial cells," relying on the description on page 8, 11, and 21. Paper No. 9 at 7. According to the Examiner, "partial differentiation," "full differentiation," and "select[ion of] individual cells expressing dopaminergic markers," is described by Luskin at pages 12, 14, 16, and 29. On these bases, the Examiner asserts the claims are anticipated by Luskin. *E.g.,* Paper No. 12.

7. In this Declaration, I provide evidence to show that neither Boss nor Luskin teaches a neuronal tissue that is made of partially differentiated neural progenitor cells that (i) maintain the capacity to perform mitosis, (ii) differentiate substantially dopaminergic neurons upon contact with specific factors, and (iii) yet does not include a population of glial cells of sufficient number to provoke an immune response when implanted into a recipient.

The Boss Reference

8. Boss teaches cell culture methods for the proliferation of "neuronal progenitor cells" *in vitro* or for the terminal differentiation of those neuronal progenitor cells into dopamine-producing cells *in vitro* or post-implantation. Col. 3, ll. 35-43. The neuronal progenitor cells described in Boss are obtained from the dopaminergic system of the brain, from an area which, *in vivo*, differentiates into a relatively high concentration of TH-positive neurons. Col. 5, ll. 25-30. The cell cultures of the Boss invention have a "loci of undifferentiated cells and loci of neurons." Col. 5, l. 53. Moreover, at least with respect to the monolayer cultures of the Boss invention, Boss teaches that, among the cells which differentiate into neurons, glial cells may also be observed. Col. 6, ll. 10-13. Boss also teaches that the neuronal progenitor cells of Boss may be induced to terminal differentiation into neurons by use of a differentiation agent that is sodium butyrate, butyric acid, cyclic adenosine monophosphate (cAMP) derivatives, phosophdiestrase inhibitors, adenylate cyclase activators and prostaglandins. Col. 13, ll. 35-50. Boss reports that upon completion of *in vitro* differentiation, the cell cultures contain "differentiated progenitor cells" that are no longer mitotic. Col. 13, ll. 66-68.

9. Moreover, the undifferentiated cell cultures of Boss are capable of differentiating into a variety of cells, such as glial cells, not just only dopaminergic neurons. In Col. 12, the passaging of neural epithelial cells is described. Under item 12, selection of specific cells using FACS or MACS is disclosed. Col. 12, ll. 53-63. Boss asserts "following growth of the neuron progenitor cell cultures for 5 -15 days, the cultures can be implanted." However, the cell selection protocol would not give rise to cells that would differentiate substantially only into dopaminergic neurons; rather, the selected cells would still possess some capability of differentiating into at least more than one type of cell, including glial cells.

10. Boss also describes the *in vitro* differentiation of the progenitor cells. Col. 13, ll. 34 - Col. 14, l. 6. The cells are exposed to a differentiation agent to achieve a terminal differentiation. According to Boss, seven days of use of the differentiation agent is optimal. Col. 13, ll. 62-63. Thus, the cells are fully differentiated and lose their ability to undergo mitosis. In Example 8, *in vitro* induction of differentiation is described. Again, the cells are exposed to the differentiation agent for seven days. *See* Example 8, Col. 19, l. 37. The method of Example 8 yields cells that are fully terminally differentiated and are therefore not capable of undergoing mitosis.

11. Thus, Boss does not report the attempt of preparation or application of a cell culture of partially differentiated neuronal progenitor cells that maintain their capacity to perform mitosis and are capable of differentiating into substantially only dopaminergic neurons.

12. Boss teaches a cell culture method that includes development of a cell culture containing undifferentiated neuronal progenitor cells into a cell culture that contains either a larger population of undifferentiated neuronal progenitor cells or a cell culture that contains undifferentiated neuronal progenitor cells and terminally differentiated dopamine-producing cells.

The Luskin Reference

13. Luskin teaches a composition that is at least about 95% mammalian, non-tumor-derived, neuronal progenitor cells that express a neuron-specific marker and which can give rise to progeny which can differentiate into neuronal cells.

14. Luskin discloses that these neuronal cells are to be derived from the anterior sub-ventricular zone of the rat brain. Pg. 7 at ll 22-23. In rats, only a fraction of cells derived from the interior sub-ventricular zone will exclusively differentiate into cells that express neuronal markers (Davies and Temple, Nature 1994; 372:263-266). All of the examples given in Luskin relate to the isolation, proliferation, differentiation, and genetic modification, and transplantation of this type of rat cells.

15. Luskin teaches that the cells can be cultured and expanded, that they are capable of dividing *in vivo* after transplantation and that the Luskin composition is a source of dividing

cells having the characteristics of neuronal cells. Pg. 12, ll. 12-13; pg. 12, ll. 15-16; pg. 13, ll. 8-10, pg. 16, ll. 13-15.

16. Example 3 describes the culturing of cells and their differentiation after plating. Since, however, the cells have not been differentiated, they are not determined, and they would differentiate into a mixture of types of neuronal cells, *i.e.*, dopaminergic, gabaergic, cholinerginic, etc. after transplantation. Thus, while each of these types of cells is a neuron or a neuronal cell, the compositions of Luskin are not substantially dopaminergic neurons.

17. The rat progenitor cells of Luskin demonstrate a rather high homogenicity of tissue, *i.e.*, they are neuronal cells, with few glial cells, and they possess some mitotic capability. They are different from the cells of the invention, however, with respect to homogenitiy of cell type and the level of determination, *i.e.*, the degree to which the cells have descended along the differentiation. In my opinion, based upon my research and knowledge of the art, it is not possible and not reported that rat or human cells derived from the sub-ventricular zone can give rise to a progeny that differentiates predominantly into only dopaminergic neurons after, for example, transplantation.

Background of the Technology Related to the Invention.

18. A common definition of stem cells yet needs to be agreed upon. German law refers to stem cells that are "(i) capable of continuous self-renewal and (ii) give rise to cells of different tissue types." This definition is in agreement with investigators (Garry et al., Curr Opin Nephrol Hypertens 2003;12:447-454)

19. "Neural progenitor cells" or "neural precursor cells," as these terms are used in the art, are cells that can be expanded and are therefore capable of continuous self renewal. In addition, almost any publication relating to neural progenitor cells or neural precursor cells has shown that a clonal expansion of such cells and subsequent differentiation gives rise to at least two tissue types, neurons and glia (Uchida et al., Proc Natl Acad Sci USA 2000; 97:14720-14725). Neural progenitor cells or neural precursor cells would therefore fulfill the definition of stem cells. Thus, neural progenitor cells or neural precursor cells are also referred to within the art as "neural stem cells."

20. The disadvantage of neural stem cells is that these cells are limited in their ability to differentiate solely into a desired specific cell type. For example, in the treatment of human disease, specific brain cells, *e.g.*, dopaminergic neurons to treat Parkinson's disease, are required. Therefore, it is important to modulate neural stem cells in such a way that they lose their stem cell character and become committed to differentiate only into one specific cell type, for example, dopaminergic neurons.

21. "Neuronal cells" and "neurons," as these terms are used in the art, are post-mitotic cells that have lost the capability of (continuous) self renewal. The loss of this capability (or the presence of the capability) is generally attributed to some as of yet unelucidated structural and/or chemical difference in the composition of the cell. As terminally differentiated cells, "neuronal cells" or "neurons" do not undergo mitosis. As a consequence, neuronal cells or neurons cannot be regarded as a source of cells for therapeutic applications such as transplantation, where expansion of the cell culture is necessary.

22. The invention of the present patent application is a new type of cell of a structural and/or chemical composition such that it is sufficiently committed to differentiate along only one pathway, such that the resultant terminally differentiated cells are solely of one type, *i.e.*, dopaminergic neurons. As is explained by the invention, the cells are prepared by transient exposure of pluripotent neural progenitor cells (stem cells that retain the structural and/or chemical structures that permit them to descend down two or more pathways of differentiation), to certain growth factors such as GNDS, LIF, IL-1, IL-11, and thyroid hormone. In preparing the patent application the cells of this invention have been referred to as "partially-differentiated neuronal progenitor cells" or "determined progenitor cells," a new terminology developed by the inventor to convey that the cells still remain capable of expansion some level of differentiation or commitment to a differentiation pathway had been developed. Thus, "partial differentiation" as used in this patent application is meant to express a reduction of pluripotency.

23. The "partially differentiated neuronal progenitor cells" differ from pluripotent neuronal progenitor cells in several aspects: They are structurally and/or chemically incapable of giving rise to more than one tissue type. They will differentiate into substantially only specific cell type, *e.g.*, dopaminergic neurons. Once determined, "partially differentiated neuronal

progenitor cells" respond to a treatment with a growth factor more rapidly than conventional pluripotent neuronal progenitor cells. When "partially differentiated neuronal progenitor cells" are exposed to a given growth factor, they do not give rise to glial tissue. In contrast, when pluripotent neuronal progenitor cells are exposed to the same growth factor, under the same conditions, the cells will, in part, differentiate into glial cells. Consequently, there is a chemical or structural aspect of the "partially differentiated neuronal progenitor cells" of the invention that is different from pluripotent neuronal progenitor cells of the prior art.

24. Moreover, the partially differentiated neuronal progenitor cells of the invention differ from terminally differentiated neuronal cells in at least that the cells of the invention are capable of undergoing mitotic division, and the terminally differentiated cells are not. This difference is a reflection of a physical and/or chemical difference between the cells, which, while as of yet unknown, does not render the difference any less significant.

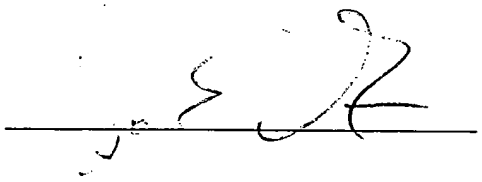
25. In addition, partially differentiated neuronal progenitor cells differ from terminally differentiated neuronal cells in that they are capable of continuous self-renewal. They maintain or gain their ability to perform mitosis in contrast the neural progenitor cells that have undergone terminal differentiation express genes related to neurogenesis or gliagenesis. During any given time of this differentiation process the self-renewing capacity is reduced compared to partially differentiated cells.

26. Thus, for at least these reasons, there is no technical or scientific basis supporting the Examiner's contention that the cell cultures of Boss which contain undifferentiated cells (capable of differentiating into more than one type of cell and/or type of neuron) and terminally differentiated neuronal cells which no longer have the capability for mitosis, or the cells of Luskin, which are capable of differentiating into any type of neuronal cell, are the same as the cell tissue of the invention.

I declare that all statements made herein are of my own knowledge and are true and that all statements made on information and belief are believed to be true; and further, that those statements were made with the knowledge that willful false statements the like so made are punishable by fine or imprisonment, or both, under § 1003 of Title 18 of the United States Code,

and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

JOHANNES SCHWARZ



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Curriculum Vitae

1981-82	Advanced studies (Violoncello, Vienna, Austria, Prof. André Navarra)
Nov. 1982- Juni 1989	Medical School in Regensburg (preclinical), Wuerzburg (clinical); Louisville, KY and Boston, MA (clinical electives)
1989 - 1996	Residency and fellowships (movement disorders, clinical electrophysiology, critical care neurology) at the Dept. of Neurology, University of Munich, Klinikum Grosshadern (Chairman: Prof. Dr. Thomas Brandt)
1996	Board certification in Neurology
1996	Certification in Clinical Neurophysiology
1996 - 1998	Associate Professor of Neurology, University of Ulm, Germany (Chairman: Prof. Dr. Albert C. Ludolph)
1997	Certification in „Intensive Care Neurology“
1998	German Habilitation (venia legendi)
1998 - 2001	Visiting Associate in Biology, California Institute of Technology (Prof. Henry A. Lester and Prof. Norman D. Davidson), sponsored by the Alexander-von Humboldt-Foundation, Germany and the Huntington Medical Research Institute, Pasadena
since 2001	Professor and vice chairman, Department of Neurology, University of Leipzig and visiting associate at the California Institute of Technology
2000	Richard-Heikkila-Award of the National Parkinson Foundation (Lester, Labarca, Schwarz)

Leipzig, January 2004

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